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PROJECT LEADER: J. I. Seeman
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I. FLAVOR RELEASE CHEMISTRY

The preparation of β -methylvaleroyl esters of sucrose by two different methods has now been completed¹, and preliminary pyrolysis results indicate that significant yields of β -methylvaleric acid are formed.² The modes of preparation for this material were the reaction of sucrose (1) with the corresponding acid and carbonyldiimidazole and (2) with N- β -methylvaleroylimidazolidine. These materials are very similar to samples provided by Flavor Development by spectroscopic analysis. Excellent results are now being obtained in even simpler modes of preparing sugar esters, i.e., by reacting sucrose directly with the related acid chloride.¹

2-Methylbutenyl ethyl 2-butylmalonate has now been prepared from the reaction of the lithium salt of 2-hydroxy-2-methylbutene and the acid chloride of ethyl hydrogen sec-butylmalonate. This important monomer will serve as an ester release polymer building block.³

The dianion of n-valeric acid was reacted with 3-pyridine-carboxaldehyde to give the β -hydroxy acid, 2-(2-butyl)-3-hydroxy-3-(3-pyridyl)propionic acid. This material was prepared as a potential aldehyde:acid release agent.³ The related ethyl ester was prepared by reacting ethyl valerate with 3-pyridinecarboxaldehyde; unfortunately, pyrolysis of this hydroxyester resulted in only low yields of the aldehyde and ester.⁴

Separate pyrolyses of the two isomers of ethyl 2-propyl-3-hydroxy-3-phenylbutanoate was carried out at 200°C. It was found that one of these was ca. three times more reactive than the other. Work is currently in progress to determine unambiguously the stereochemistry of the two isomers.⁴

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Using a literature procedure, *l*-tartatic acid was converted to *l*-bis-*O*-carboxytartaric anhydride, a rather remarkable organic molecule having the unusual empirical formula $C_6H_2O_8$. Perhaps not unsurprising, it may find utility for a dry powder soft drink carbonating ingredient. Samples will soon be forwarded to Dr. Will for evaluation.³

Efforts to prepare 2-(2-butyl)-3-hydroxy-3-(3-pyridyl)-butanoic acid in large scale were somewhat thwarted by unusual experimental problems but work is underway to overcome these. However, the related ethyl 2-(2-butyl)-3-hydroxy-3-phenylbutanoic acid was prepared again and added to the CR file.⁵ Additional quantities of sodium menthyl itaconate have been prepared for flavor development evaluations.³

Benzyl and β -phenylethyl itaconate monomers were synthesized and subsequently independently polymerized.⁶ GPC analysis indicates that they are 90% polymer/10% monomer each.⁷ Various procedures have been tried to make the related phenol and dimethyl allyl alcohol esters without success, though some promise comes from the reaction of lithium phenoxide (2 equiv) with itaconyl chloride.⁶

Successful formation of the vinyl carbonate monomer of an unsaturated ester release system has been completed. This material has also been polymerized, giving the first example of a release agent for this class of flavorant.⁶

II. FLAVOR CHEMISTRY

A total of 15 g of 12-(*Z*)-abienol, an important terpenoid precursor to a wide range of labdanoid flavorants, has been obtained. A portion of abienol was photooxygenated and the crude product isolated by column chromatography. The mixture of oxygenated terpenoids has a "delightful dusty-wood aroma"; it is hoped that we will be able to separate out materials known to be important tobacco flavorants. The remaining abienol was treated with *m*-chloroperbenzoic acid to give, following HPLC purification, a mixture of two major constituents. This is another effort to prepare important oxygenated terpenoids.⁸

Small quantities of isopropylpyrazine and *t*-butylpyrazine have been synthesized. A practical synthesis of 2-chloro-3-methylpyrazine was also developed. This latter compound should serve as the key intermediate in the preparation of 2,3-dialkylated pyrazines.⁸ These will form a series of compounds to be used in a multidimensional scaling experiment with Dan Ennis from which it is hoped to correlate subjective properties pyrazine flavorants with their structure and chemical reactivity.

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Thuja leaf oil, comprising ca. 50% thujone, was oxidized with permanganate to give a trisubstituted, poly oxygenated cyclopropane derivative which was treated with water to form 3-isopropyl-6-ketohept-2-enoic acid. Solanone was obtained in initial experiments in one step from the reaction of 2-isopropyl-5-ketohexanal and an allylic Wittig reagent. Efforts to purify solanone are underway.⁹

A number of ketoacids were added to the CR file, and the related invention record for the preparation (process) of such compounds has been submitted.¹⁰

After much effort, 2-isopropylbutanal, a key compound in the preparation of numerous tobacco identical terpenoid flavorants, has been obtained. The successful route involved the ethylation of the *t*-butylimine of isovaleraldehyde. Work is in progress to improve the low yield.¹⁰

III. ALKALOID CHEMISTRY

With the assistance of Steve Haut, the successful use of HPLC for the purification of nicotine analogue reaction products has been successful. This is an important accomplishment, for it will allow us to prepare many nicotinoids heretofore unavailable. Thus, cis and trans-3'-methylnicotine have been obtained in sufficient quantities for testing. Several purifications of 2-, 4- and 6-methylnicotine having all three products in the total mixture were accomplished by HPLC and optically active 2-methylnicotine and 6-methylnicotine have now been obtained for the first time. The rotations were low in some cases, high in others, indicating that racemization may be occurring during the reaction. Work continues along these lines.^{11,12}

6-Methylnicotine was reacted with LDA/THF and gaseous formaldehyde to give in 43% yield a hydroxyethylnicotine. This compound is the first heteroatom substituted alkyl nicotine and is to be used to prepare a nicotine analogue which will react irreversibly and covalently at the nicotine receptor. Should this approach succeed, a major step toward isolating and identifying the nicotine receptor(s) will have been made. A side product in the above reaction may be 6-hydroxymethyl-nicotine, a very interesting compound in its own right.¹¹

Additional quantities of 4-isonicotine and a number of quaternary salts have been prepared. Also, efforts to prepare a tetradeutero analogue of 3,3'-isonicotine are meeting with success. The latter compound will be useful in analyzing the alkylation of this interesting active material.¹²

We have most recently found¹³ that 2'-methylnicotine is a most unusual nicotinoid. Efforts are underway to prepare additional 2'-substituted nicotine analogues in order to evaluate

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their structure-activity relationships.¹²

Nitroethylene has now been found to be an excellent Michael acceptor, having reacted to give in reasonable yield 6-nitroethyl-7,8-dihydro-5(6)-quinolone, an intermediate to the 2,2'-bridged nicotinoids. This procedure will allow us to convert 3-acetylpyridines to the corresponding nicotine compound. Racemization studies continue on our asymmetric synthesis of 5-methylnicotine.¹¹

The iodomethylations of four 1-methyl-2-(2-alkylphenyl)-pyrrolidines were carried out as well as of a number of other nicotine analogues including 2'-methylnicotine. Standard curves were also obtained on eight compounds.¹⁴

IV. CUSTOM SYNTHESIS

A mixture containing the tobacco beetle pheromone has now been prepared, based on detailed mass spectral evaluations. This mixture was obtained in seven steps from diethyl ketone. A major effort in purification has begun. It is hoped that individual isomeric entities can be given to A. Manzelli and S. Long such that the stereochemical structure of the pheromone can be ascertained. Large scale preparation of this material is in progress.¹⁰

V. REFERENCES

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